PATENT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF WITHDRAWAL OF PRIORITY CLAIM

(PCT Rule 90*bis*.3 and Administrative Instructions, Section 415(a) and (b))

To:

STOTT, Michael, J.
Glaxo Wellcome plc
Glaxo Wellcome House
Berkeley Avenue
Greenford
Middlesex UB6 0NN
ROYAUME-UNI

Date of mailing (*day/month/year*) 21 January 2000 (21.01.00)	
Applicant's or agent's file reference PU3513	**IMPORTANT NOTIFICATION**
International application No. PCT/EP99/05271	International filing date (*day/month/year*) 23 July 1999 (23.07.99)
Applicant GLAXO GROUP LIMITED	

1. The applicant is hereby notified that **the priority claim made in the international application has been withdrawn** in accordance with a notice of withdrawal received from the applicant on:

   20 January 2000 (20.01.00)

   The attention of the applicant is drawn to the fact that the withdrawal of the priority claim will result in the re-calculation of time limits which have not already expired (see Rule 90*bis*.3(d)).

2. ☐ In the case where **multiple priorities** have been claimed, the above action relates to the following priority claim(s):

3. A copy of this notification has been sent to the receiving Office and to:

   ☒ the International Searching Authority *(where the international search report has not yet been issued)*

   ☒ the designated Offices *(which have already been notified of the receipt of the record copy)*

   ☐ the International Preliminary Examining Authority

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Dorothée Mülhausen
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 April 2001 (04.04.01)	
International application No. PCT/EP99/05271	**Applicant's or agent's file reference** PU3513
International filing date (day/month/year) 23 July 1999 (23.07.99)	**Priority date** (day/month/year)
Applicant KNICK, Vincent, C. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 February 2001 (15.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Zakaria EL KHODARY

Telephone No.: (41-22) 338.83.38

Copy for the Elected Office (EO/US)

PCT/EP99/05271

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

STOTT, Michael, J.
GlaxoSmithKline
Corporate Intellectual Property
Two New Horizons Court
Middlesex TW8 9EP
ROYAUME-UNI

Date of mailing (day/month/year)
17 August 2001 (17.08.01)

Applicant's or agent's file reference
PU3513

IMPORTANT NOTIFICATION

International application No.
PCT/EP99/05271

International filing date (day/month/year)
23 July 1999 (23.07.99)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

STOTT, Michael, J.
Glaxo Wellcome plc
Glaxo Wellcome House
Berkeley Avenue
Greenford
Middlesex UB6 0NN
United Kingdom

State of Nationality:

State of Residence:

Telephone No.
0171 493 4060

Facsimile No.
0181 966 8838

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

STOTT, Michael, J.
GlaxoSmithKline
Corporate Intellectual Property
Two New Horizons Court
Middlesex TW8 9EP
United Kingdom

State of Nationality:

State of Residence:

Telephone No.
020 8966 8412

Facsimile No.
020 8966 8838

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Maria Victoria CORTIELLO

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004218787

Copy for the Elected Office (EO/US)

PCT/EP99/05271

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

STOTT, Michael, J.
GlaxoSmithKline
Corporate Intellectual Property
(CN9.25.1)
980 Great West Road
Brentford
Middlesex TW8 9GS
ROYAUME-UNI

Date of mailing (day/month/year)
18 February 2002 (18.02.02)

Applicant's or agent's file reference
PU3513

IMPORTANT NOTIFICATION

International application No.
PCT/EP99/05271

International filing date (day/month/year)
23 July 1999 (23.07.99)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
STOTT, Michael, J.
GlaxoSmithKline
Corporate Intellectual Property
Two New Horizons Court
Middlesex TW8 9EP
United Kingdom

State of Nationality

State of Residence

Telephone No.
020 8966 8412

Facsimile No.
020 8966 8838

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
STOTT, Michael, J.
GlaxoSmithKline
Corporate Intellectual Property
(CN9.25.1)
980 Great West Road
Brentford
Middlesex TW8 9GS
United Kingdom

State of Nationality

State of Residence

Telephone No.
020 8047 5000

Facsimile No.
020 8047 6894

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Sangeeta JAIYA

Telephone No.: (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PU3513

Box No. I TITLE OF INVENTION

Antibody Combination

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below).*

Glaxo Group Limited
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex, UB6 0NN
GB

☐ This person is also inventor.

Telephone No. 0171 493 4060

Facsimile No. 0181 966 8838

Teleprinter No. 25456

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KNICK, Vincent C
Glaxo Wellcome Inc
Five Moore Drive
Research Triangle Park
NC 27709
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country).*

STOTT, Michael J
Glaxo Wellcome plc
Glaxo Wellcome House, Berkeley Avenue
Greenford, Middlesex
UB6 0NN
GB

Telephone No.:
0171-493-4060
Facsimile No.:
0181-966-8838
Teleprinter No.:
25456

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Express Mail Label No. EL395894335US

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

STIMMEL, Julie Beth
Glaxo Wellcome Inc
Five Moore Drive
Research Triangle Park
NC 27709
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

THURMOND, Linda M
Glaxo Wellcome Inc
Five Moore Drive
Research Triangle Park
NC 27709
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

See Notes to the request form

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked):*

Regional Patent

☑ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☑ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☑ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☑ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*.....

National Patent *(if other kind of protection or treatment desired, specify on dotted line):*

☑ **AL** Albania.....
☑ **AM** Armenia.....
☑ **AT** Austria.....
☑ **AU** Australia.....
☑ **AZ** Azerbaijan
☑ **BA** Bosnia and Herzegovina .....
☑ **BB** Barbados
☑ **BG** Bulgaria.....
☑ **BR** Brazil.....
☑ **BY** Belarus.....
☑ **CA** Canada
☑ **CH and LI** Switzerland and Liechtenstein
☑ **CN** China.....
☑ **CU** Cuba.....
☑ **CZ** Czech Republic.....
☑ **DE** Germany.....
☑ **DK** Denmark.....
☑ **EE** Estonia.....
☑ **ES** Spain.....
☑ **FI** Finland.....
☑ **GB** United Kingdom
☑ **GD** Grenada
☑ **GE** Georgia.....
☑ **GH** Ghana.....
☑ **GM** Gambia
☑ **HR** Croatia .....
☑ **HU** Hungary.....
☑ **ID** Indonesia
☑ **IL** Israel.....
☑ **IN** India.....
☑ **IS** Iceland
☑ **JP** Japan.....
☑ **KE** Kenya.....
☑ **KG** Kyrgyzstan.....
☑ **KP** Democratic People's Republic of Korea.....
☑ **KR** Republic of Korea.....
☑ **KZ** Kazakstan.....
☑ **LC** Saint Lucia
☑ **LK** Sri Lanka
☑ **LR** Liberia
☑ **LS** Lesotho.....
☑ **LT** Lithuania
☑ **LU** Luxembourg
☑ **LV** Latvia
☑ **MD** Republic of Moldova.....
☑ **MG** Madagascar.....
☑ **MK** The former Yugoslav Republic of Macedonia .....
☑ **MN** Mongolia
☑ **MW** Malawi.....
☑ **MX** Mexico.....
☑ **NO** Norway
☑ **NZ** New Zealand.....
☑ **PL** Poland.....
☑ **PT** Portugal.....
☑ **RO** Romania
☑ **RU** Russian Federation.....
☑ **SD** Sudan
☑ **SE** Sweden
☑ **SG** Singapore
☑ **SI** Slovenia.....
☑ **SK** Slovakia.....
☑ **SL** Sierra Leone
☑ **TJ** Tajikistan.....
☑ **TM** Turkmenistan.....
☑ **TR** Turkey.....
☑ **TT** Trinidad and Tobago.....
☑ **UA** Ukraine.....
☑ **UG** Uganda.....
☑ **US** United States of America.....
☑ **UZ** Uzbekistan.....
☑ **VN** Viet Nam.....
☑ **YU** Yugoslavia.....
☑ **ZW** Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

☑ **AE** United Arab Emirates
☑ **ZA** South Africa
☐.....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box

Filing Date of Earlier Application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 27 July 1998 (27.07.98)	9816280.3	GB		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s):_____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earli application was filed (Rue 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA/

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):* Date *(day/month/year)* Number Country *(or regional office)*

Box. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	4
description (exlcuding sequence listing part	34
claims	2
abstract	1
drawings	24
sequence listing part of description	37
Total number of sheets	102

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify):*

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Michael J Stott
Agent for the Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application
2. Drawings ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau

PCT
FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference PU3513

Applicant

Glaxo Group Limited et al

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . EUR102 [T]

2. SEARCH FEE ..... EUR1124 [S]

Internation Search to be carried out by_____

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application 102 sheets.

first 30 sheets . . . . . EUR413 [b_1]

72 remaining sheets x 10 additional amount = EUR720 [b_2]

Add amounts entered at b_1 and b_2 and enter total at B . . . . . EUR1133 [B]

Designation Fees

10 number of designation fees payable *(maximum 11)* x 95 amount of designation fee = EUR950 [D]

Add amounts entered at B and D and enter total at I . EUR 2083 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicant are) so entitled, the total to be entered as I is 25% of the sumof the amounts entered at B and D.

4. FEE FOR PRIORITY DOCUMENT . . . . . [P]

5. TOTAL FEES PAYABLE EUR3309

Add amounts entered at T, S, I and P,and enter total in the TOTAL box ..... TOTAL

☐ The designation fee is not paid at this time

MODE OF PAYMENT

☒ authorization to charge deposit account (see below)
☐ bank draft
☐ coupons
☐ cheque
☐ cash
☐ other (specify)
☐ postal money order
☐ revenue stamps

Deposit Account Authorization *(this mode of payment may not be available at all receiving Offices)*

The RO/

☒ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

28050185
Deposit Account Number

20 July, 1999
Date *(day/month/year)*

Signature Michael J STOTT
Agent for the Applicants

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

STOTT, Michael J.
GLAXO WELLCOME PLC
Glaxo Wellcome House
Berkeley Avenue
Greenford
Middlesex UB6 0NN
GRANDE BRETAGNE

03 MAY 2001

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	03.05.2001
Applicant's or agent's file reference PU3513	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/05271	23/07/1999	27/07/1998

Applicant
GLAXO GROUP LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Neumann, M Tel.+49 89 2399-7351

Form PCT/IPEA/416 (July 1992)

Express Mail Label No.
EL395894335US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PU3513		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/05271	23/07/1999	27/07/1998
International Patent Classification (IPC) or national classification and IPC A61K39/395		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/02/2001	03.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mennessier, T Telephone No. +49 89 2399 8687

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/05271

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-34 as originally filed

Claims, No.:

1-15 as originally filed

Drawings, sheets:

1/24-24/24 as originally filed

Sequence listing part of the description, pages:

1-37, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 12-14.

because:

   ☒ the said international application, or the said claims Nos. 12-14 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive st p or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-6 and 13
	No:	Claims	1-3, 7-12, 14 and 15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-11 and 15
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Documents cited in this written opinion

Reference is made to the following documents:

D1: *Hybridoma*, 5(suppl. 1), 1986, S171-4, XP000881980

D2: *International Journal of Cancer*, 71(2), 1997, 237-45, XP000882050

D3: *Cancer Investigation*, 17(suppl. 1), 1999, 32-34, XP000882015

2. Comments with respect to item III

Claims 12-14 relate to methods of treatment of the body by therapy, i.e., to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3. Comments with respect to item V

a) Novelty (Article 33(2) PCT)

Document D1 (see the whole document) discloses a "combination" consisting of an 17-1A monoclonal antibody and three chemotherapeutic agents, namely 5-fluorouracil, Adriamycin and mitomycin, as generally defined in **claims 1 and 2**. Therefore, the subject-matter of the said claims lacks novelty. As the term "Panorex" referred to in claim 3 is used to designate a particular 17-1A antibody, also the subject-matter of **claim 3** is not new. As the cells treated in document D1 are adenocarcinoma cells capable of metastasing, the same conclusion also applies to **claims 7-9**. As the "combination" of drugs was used in D1 to treat advanced pancreatic carcinoma, the subject-matter of **claims 10-12, 14 and 15 is** considered to lack novelty.

b) Inventive step (Article 33(3) PCT)

(i) The present comments are made with respect to claims for which novelty can be acknowledged, i.e., **claims 4, 5, 6 and 13**.

(ii) It may be considered that a skilled person aware of document D1 would be prompted to test further chemotherapeutic agents available to him at the priority date in view of preparing a further "combination" as already described in D1 and to test it as also done in D1 in the treatment of tumoral cells. Therefore, the subject-matter of **claims 4 and 5** appears not to involve an inventive step.

(iii) Novelty of claim 13 has been acknowledged on the basis of an additional technical feature which is based on the measuring of a parameter which had not been taken into consideration by the authors of document D1. In the absence of any data suggesting that binding of the 17-1A monoclonal antibody of document D1 would not be less than between 2 to 10 fold compared to binding in the absence of a chemotherapeutic agent to be used in combination, it cannot be concluded that the subject-matter of **claim 13** involves an inventive step.

(iv) Moreover, the point has to be stressed that in document D2 (see the two chapters entitled "Modulation of antigen expression" on pages 238-239 and pages 239-240, respectively) it has been unambiguously established that pre-incubation of two tumour cell lines in presence of 5-fluorouracil results in an increase in EGP40 expression, which is a clear indication to a person skilled in the art, that administration of a "combination" as defined in claim 1, of which the chemotherapeutic agent being administered prior to the antibody (see point 6(b) below), [the only administration mode of the invention for which a true support exists in the description] would reasonably be more efficient than administration of the antibody alone. The said person would therefore not have regarded as surprising the finding (as referred to in the paragraph bridging pages 3 and 4 of the description) on which the

invention as a whole has been said to rely.

(iv) In view of the above remarks, it is therefore considered that none of the claims involves an inventive step.

c) Industrial applicability (Article 33(4) PCT)

(i) The subject-matter of **claims 1-11 and 15** is considered to be susceptible of industrial applicability.

(ii) For the assessment of the present **claims 12-14** and also **claims 10-11** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

d) P-document

Should the priority appear not to have been validly claimed, document D3 would have to be taken into consideration when examining whether the various aspects of the claimed invention are new and involve an inventive step.

4. Comments with respect to item VII

a) In **claims 4 and 5** the use of abbreviations (see the terms "UFT, CPT-II, 5FU") to designate chemotherapeutic agents should be avoided. The same also applies to trademarks (see the term "Raloxiden").

b) The use of the terms "*continuous infusion*" in each of **claims 4 and 5**, and of the term "*iv and oral*" in claim 4 appears to be irrelevant.

c) Taken into consideration the fact that in **claim 4** which is dependent on **claim 1** the chemotherapeutic agent referred to is defined as consisting of one or more agents, in order to avoid any ambiguity it would have been more appropriate to indicate in **claim 1** that the subject-matter for which protection is sought is a combination of an antibody "with one or more chemotherapeutic agents".

5. Comments with respect to item VIII

a) Due to the use of the term "*combination*", which appears in the present context to be vague and indefinite, **claims 1-9** are objected to under Article 6 PCT. Reformulation of the said claims in such a way that they appear to be unambiguously directed to a preparation in the form of a "kit-of-parts", of which the components formed a functional unity through a purpose-directed application, would overcome the objection.

b) What the description clearly establishes (see Examples 2 to 5) is that pre-treatment of tumour cells with a chemotherapeutic agent known to block cell cycle progression at S and/or G_2/M results in a significant increase in the density of the Ep-CAM antigen population and thus in greater targeting of anti-Ep-CAM antibodies to Ep-CAM expressing tumours. This is the gist of the invention, see further the paragraph bridging pages 3 and 4 of the description. It has not been established elsewhere in the description how a chemotherapeutic agent and an anti-Ep-CAM antibody could react synergistically in the case where either the agent and the antibody are administered simultaneously or the antibody is administered prior to the agent. Therefore, administration of the agent prior to the antibody has to be regarded as an technical feature that is essential to the performance of the invention and as such should be present in each of use and method **claims 10-14**, which presently are objected to under Article 6 PCT as not containing the said feature.

c) **Claim 15** appears to lack clarity due to the omission of a verb after the term "*composition*". Moreover, in order to meet the requirements of Article 6 PCT, for the reasons explained above, **claim 15** should be re-formulated in such a

way that it is clearly specified that the claimed composition contains both an antibody and a chemotherapeutic agent which are physically separated, the said separation allowing the agent to be administered prior to the antobody.

d) The wording of **claim 5** appears to be confusing due to the use of the term "*and*". It is not clear whether the claimed combination comprises only one of the listed chemotherapeutic agents or each of them. For that reason, **claim 5** is also objected to under Article 6 PCT.

e) According to page 7, lines 28-30 "*throughout the specification the term chemotherapeutic can [therefore] be substituted with "radiotherapy"*". This appears to be a non-admissible statement, as, indeed, chemotherapy and radiotherapy involve two distinct treatments, each of the terms having a well- recognized specific meanings. If the Applicants were intended to seek protection for the use of an antibody as defined in claim 1 in combination with radiotherapy, they should have filed further claims specifically directed to that subject-matter. Nevertheless, in the absence of any experimental evidence elsewhere in the description with regard to the said subject-matter, said claims would have been considered not to be supported by the description. In order to avoid any discrepancy between the claims and the description, the whole paragraph of the description on page 7, lines 25-30 should be deleted.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PU3513		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/05271	23/07/1999	27/07/1998
Applicant		
GLAXO GROUP LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   COMBINATION OF AN ANTI-EP-CAM ANTIBODY WITH A CHEMOTHERAPEUTIC AGENT

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures

INTERNATION EARCH REPORT

International application No.
PCT/EP 99/05271

Box I Obs rvations where c rtain claims w re found uns archable (Continuation of item 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the co-administered chemotherapeutic agent and anti-Ep-CAM antibody.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]EP 99/05271

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/395 //A61K38:16,A61K31:00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAUL A R ET AL: "Treatment of advanced measurable or evaluable pancreatic carcinoma with 17-1A murine monoclonal antibody alone or in combination with 5-fluorouracil, adriamycin and mitomycin (FAM)." HYBRIDOMA, (1986 JUL) 5 SUPPL 1 S171-4. , XP000881980 the whole document --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2000	14. 04. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mennessier, T

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KIEVIT E ET AL: "Determination of tumor-related factors of influence on the uptake of the monoclonal antibody 323/A3 in experimental human ovarian cancer." INTERNATIONAL JOURNAL OF CANCER, (1997 APR 10) 71 (2) 237-45. , XP000882050 page 238, right-hand column -page 240, left-hand column page 243; table III	1-15
Y	BOKEMEYER C ET AL: "[Current aspects of adjuvant and palliative chemotherapy in colorectal carcinoma]. Aktuelle Aspekte zur adjuvanten und palliativen Chemotherapie beim kolorektalen Karzinom." SCHWEIZERISCHE RUNDSCHAU FUR MEDIZIN PRAXIS, (1997 SEP 24) 86 (39) 1510-6 REF: 11 , XP000882022 page 1515, paragraph 3.4; table 8	1-15
Y	CASILLAS S ET AL: "Adjuvant therapy for colorectal cancer: present and future perspectives." DISEASES OF THE COLON AND RECTUM, (1997 AUG) 40 (8) 977-92. REF: 80 , XP000882030 page 989, left-hand column page 980; table 1	1-15
Y	EP 0 252 741 A (CENTOCOR INC) 13 January 1988 (1988-01-13) page 2, line 58-63 page 3, line 8-13	1-15
A	BLEIBERG H: "Continuing the fight against advanced colorectal cancer: new and future treatment options." ANTI-CANCER DRUGS, (1998 JAN) 9 (1) 18-28. REF: 83 , XP000882025 page 23 page 24; table 1	1-15
A	ELIAS D J ET AL: "Monoclonal antibody KS1/4-methotrexate immunoconjugate studies in non-small cell lung carcinoma." AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (1994 OCT) 15 (4) 1114-22. , XP000882026 page 1114 page 1121, left-hand column	1-15

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HAISMA H J ET AL: "A monoclonal antibody-beta-glucuronidase conjugate as activator of the prodrug epirubicin-glucuronide for specific treatment of cancer." BRITISH JOURNAL OF CANCER, (1992 SEP) 66 (3) 474-8. , XP000882039 the whole document ---	1-15
P,X	SCHWARTZBERG, LEE S. (1): "Chemotherapy plus PANOREX (17-1A monoclonal antibody) as adjuvant therapy for colon cancer: Ongoing studies." CANCER INVESTIGATION, (1999) VOL. 17, NO. SUPPL. 1, PP. 32-34. MEETING INFO.: XVI CHEMOTHERAPY FOUNDATION SYMPOSIUM ON INNOVATIVE CANCER THERAPY FOR TOMORROW NEW YORK CITY, NEW YORK, USA NOVEMBER 11-13, 1998 CHEMOTHERAPY FOUNDATION. , XP000882015 the whole document -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
[redacted]/EP 99/05271

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0252741 A	13-01-1988	AT 159174 T	15-11-1997
		DE 3752129 D	20-11-1997
		DE 3752129 T	07-05-1998
		EP 0755683 A	29-01-1997
		ES 2110392 T	16-02-1998
		GR 3025902 T	30-04-1998
		HK 1002829 A	18-09-1998
		JP 2979318 B	15-11-1999
		JP 63060941 A	17-03-1988
		JP 2000026312 A	25-01-2000

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
GLAXO WELLCOME PLC
Glaxo Wellcome House
Attn. STOTT, Michael J.
Berkeley Avenue
Greenford
Middlesex UB6 ONN
UNITED KINGDOM

Global Intellectual Property
RECEIVED 17 APR 2000 INIT DH
ACTION 14/6/00 ATTN GN FILE GW

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)* 14/04/2000

Applicant's or agent's file reference
PU3513

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/EP 99/05271

International filing date *(day/month/year)* 23/07/1999

Applicant
GLAXO GROUP LIMITED et al.

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Véronique Baillou

Express Mail Label No.
EL395894335US

NOTE FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.